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Thesis

THE SMALL BLOOD VESSELS
OF THE MAMMAL

by

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THE SMALL BLOOD VESSELS OF THE MAMMAL

The fact that in the literature there is only one classic monograph on the small vascular vessels of the animal body, "The Anatomy and Physiology of Capillaries" by August Krogh, 1929, indicates the fact that the study of the smallest blood vessels has been neglected. It is the object of this communication to review the work which in the last two decades has been done on the physiology of these vessels, namely, the arterioles, capillaries, and venules.

It is assumed that definitions of the primary entities, the arterioles and venules, are not required here. In the case of the capillaries, however, one is forced to give a definition, because around

the concept of the capillary, the most minute unit of the vascular system, there seems to exist an aura of inexact terminology. In the usage of Best and Taylor, 1943, the term capillary will here designate all the purely endothelial tubing which lies between the arterioles on one side and the venules on the other. It appears, especially among clinicians, that this term possesses a general and wide application, referring usually to all of the small blood vessels, but here the word will be used only in the strict anatomical sense.

The major part of the present knowledge of the smallest blood vessels has been worked out on the representative lower vertebrates, and information from the mammals has only recently come to be accepted. In view of the many clinical implications for this group, as well as for the ultimate truth of biology and physiology, this review is primarily devoted to the micro-vascular physiology of the Mammalia, not without, however, reference to researches upon other animal types.

METHODS AND TECHNIQUES

The biologist, in studying the small blood vessels, is faced with the difficulty of securing an optically suitable field of observation, which will at the same time include as much of the physiological environment as is possible. In a lower vertebrate, such as the frog, observation of capillary tracts, for example, is made considerably more convenient and precise by several structures which lend themselves well to this purpose. The mesentery, the retrolingual membrane (that is, the lymph sac on the ventral surface of the tongue), and the web of the foot have all been utilized in living vessel research. But in the mammal similar techniques

have not always proved satisfactory or possible, and new methods have been devised which seem to meet the existing needs. The following discussion outlines the two chief techniques for mammals, the Clark window or ear chamber method for laboratory animals, and capillaroscopy of human subjects. Other methods, usually physiological, will be reviewed as the particular phases of the discussion demand.

THE CLARK EAR CHAMBER. In the examination of living tissues, the prime requisite is that the tissue be thin enough to transmit sufficient light for microscopic examination. In the lower vertebrates, tissues and organs complying with this requirement are readily available. In the mammal, however, this condition is the exception rather than the rule. The bat's wing and the ear of the white mouse, cat, and young albino rat have been used. But the thickness and opacity of these tissues, not to mention the presence of hair and epidermal pigmentation, contrive to make these structures practically useless for observations of individual cell development and behavior, such as is required in a study of the blood vessels. The mesentery of certain mammals has likewise been used, but the unphysiological exposure of this membrane, in addition to the required anesthesia of the subject, prevents an efficient use of this possibility in these larger animals. This problem led Sandison, 1928, to develop a method introduced in 1875 by Ziegler and in 1902 by Maximow. The technique consisted, in principle, of two pieces of glass fastened together so that the intervening space permitted the ingrowth of living tissues with all the cellular elements. Such an apparatus permitted the worker to make microscopic observations in vivo, but not without certain technical difficulties. The growing and expanding tissues within the

"chamber" inevitably forced apart the component plates, glass in the first instruments or mica in the case of Sandison's improvement. In time celluloid was found to be an almost ideal material for the chambers, and the original mica and glass were abandoned in its favor. Sandison found that two plates of celluloid could be cemented together without the use of screws, the screws being an obstacle to the use of the microscope objective. Furthermore, the celluloid proved to be more transparent, and was unique in that almost any size, shape, or form of chamber could be manufactured from the basic material. But certain difficulties still occurred in the use of the ear chamber. Clark and his co-workers, 1930, produced a modification designed to counteract these discrepancies. In the first place, the new chamber of Clark was changed in shape to either oval or circular. The sharp, square corners of the previous models invariably, sooner or later, cut through the skin. Protective collars of celluloid were added to prevent drying and retraction of the cut edges of the skin. More auricular cartilage was included also, an improvement which gave added strength and stability to the ear preparations. Clark returned to Sandison's early method of bolting, but also retained the cementing principle, a method of fusing the celluloid plates with an ether-alcohol solvent. This modification was made as an effort to obtain an uniformly thin space for oil-immersion study purposes, but again trouble arose because thin celluloid is permeable to moisture, and drying of the tissues in the chamber occurred. In order to prevent this dehydration, Clark again utilized mica. Certain of the early difficulties with this plastic were largely obviated by the new improved technique.

Clark, 1930, described the various forms of the ear chamber which

are available for different problems of study. (1) The bay chamber derives its name from the thin observation spaces or bays punched in the celluloid floor of the chamber; these are in contrast with the central elevated tables of the other chambers. These bays are described as very shallow (only about 0.75 micron deep) and connect through tunnels with a groove made for the large artery always included in the preparation. The two main plates of the chamber are then fused by solvent everywhere except the depressed bay areas. An outer collar contains a moist pledget of cotton in an attempt to prevent drying. This arrangement was recommended for long-continued observation of new-growing capillaries and of blood cells in a region undisturbed by motion, pulling, and tension upon the tissue, and also, with modification, for studies of the effect of chemical substances upon living cells and vessels. (2) In the round-table chamber, the top or observation side of the chamber is made of mica, the chambers being fastened together at the time of operation by means of bolts. In the center of the chamber is a "round table" of celluloid, resting upon and attached to the floor of the chamber, and upon which the thin observation layer of tissue rests. The major part of the space in the chamber is reserved for ear cartilage. This type of chamber may be constructed so that transplants of tissues may be made through an entry in the central table at its base. The round table chamber is planned for studies on new growth of both blood vessels and lymphatics, small blood vessel development and differentiation, and for the cytological examination of blood cells and cells of connective tissue. (3) The pre-formed tissue chamber was devised for the purpose of obtaining a thin, transparent area in which preformed vessels with their original nerve supply could be studied and compared with new growing vessels. This

modification, according to Clark, has proved valuable especially in physiologic studies of the circulation. Here is retained a layer of skin and all of its blood vessels, nerves, and other tissues, with the substitution of a thin mica covering for the cartilage and skin of the other side. This modification of the ear chamber is best adapted for physiological and pharmacological experiments on blood vessels, where it is essential that the nerve supply and surrounding tissues be intact. (4) The principle of the "preformed tissue chamber" is included in the so-called combination chamber, in which it is possible to compare living preformed blood vessels, which are present before the addition of the chamber, and new growing vessels. In the combination chamber there is an area in the center for the observation of new-growing vessels, and a peripheral area in which the preformed vessels are preserved, new growth taking place in the center. Because, however, of the rapid epidermal regeneration, this form of chamber is really only useful for short-time studies, that is, a week to ten days in length, but the preparation is an excellent one for studies of structure and contractility in both old and new vessels.

Sanders, Ebert, and Florey, 1940, criticized the Clark celluloid chambers for the thickness of the center table over which the tissue to be observed grows. Claiming that the full numerical aperture of the microscope condenser could not be used, these workers planned a chamber which enabled complete use of both the condenser and the oil-immersion lens. Their improvement consisted of substituting, for the base of the chamber, sheet silver 0.6 mm. thick, in the center of which is a hole into which fits a disc of plastic 1.1 mm. thick. This decreases the depth ordinarily presented by the typical Clark chamber, and the workers reported optically clear results, an objective not obtainable with the ordinary thick tissue

growth of the Clark chamber.

The most recent modification of the Clark chamber was reported by Levinson and Essex, 1943. Their type of chamber is fashioned on a lathe from lucite plastic. The authors described the following advantages, over the original Sandison chamber, to their modification: (1) lucite does not warp, (2) is more transparent, and (3) may be used repeatedly is desired.

The round table chamber has been equipped to study controlled temperature changes. Beecher, 1936b, reported the apparatus equipped with a relatively deep collar, so that the chamber is capable of holding water. The chamber is attached to a drain from the reservoirs, and is itself drained by a second pipelet. Another specialized kind of chamber, designed for permeability studies, the moat chamber or "filter disc chamber," was originally described by Abell and Clark, 1932. In this device, as in the typical ear chamber, capillaries, both developing and mature, can be seen with the high power of the microscope, their condition recorded, and their area calculated. Nitrogenous substances which permeate the walls of the capillaries diffuse into a reservoir or moat, containing a known volume of physiologic saline, from which the entire solution can be removed and analyzed. A recent use of this chamber was reported by Abell, 1939.

The operative procedure for the insertion of the chamber, according to Clark, op. cit., may be noted. Strict asepsis is maintained in the surgery. The ear area is prepared by clipping and shaving, so that the distal two-thirds on both sides of the auricle are clean. Disinfection with one percent phenol or 1:2500 metaphen solution is used, but strong disinfectants or depilatories are avoided since the rabbit's ear is tender and the skin easily injured. Anesthesia is provided by either

cocaine or novocaine. Sterilization of the chamber is secured by a full-strength hexyl resorcinol or 1:500 metaphen bath. Washing of the operated area or of instruments and apparatus is done with either sterile Ringer's saline or sterile distilled water as the particular case may demand. The dissection is so carried out that the central artery of the ear is protected.

Beecher, 1936a, made some radical departures from Clark's recommendations on technique. The use of chemical depilatories, according to Beecher, removes hair more efficiently than does shaving, but he did not allow for any harmful effects of such agents. He suggests that acetone or ordinary nitro-cellulose household cement are both better for use in attaching the chamber plates than is the original alcohol-ether mixture. The actual operative procedures on the ear are done at one sitting instead of taking the time required by Clark's method.

The chamber technique, originally planned for the ear, has been developed for another part of the animal body. Williams, 1934, at the suggestion of Clark, devised a technique wherein a flap of body wall skin can be removed at one end, with the other end attached to the body and its normal blood and nerve supply. Into this flap a transparent chamber is inserted.

While the Clark ear chamber was developed for use on the rabbit, other writers have studied the device when employed on other mammals. Moore, 1936, suggested several distinct differences between the reactions of the rabbit and the responses of the dog to the inserted ear chamber. In the dog Moore reported that the skin surface did not dry and adhere to the celluloid surfaces of the chamber as was the case in the rabbit.

Also, the formation of fibrin and its subsequent gelatinization in the growth area was at a minimum as compared to the similar situation in the rabbit. On the other hand, connective tissue forming in the rabbit chamber gave a firm support, but in the dog the character of the preparation was soft and flabby due to the loose network of fibers growing into the prepared area.

CAPILLAROSCOPY. In the human subject examination of the minute blood vessels is an almost impossible task due to the inaccessibility of these structures, but some observations are possible by "capillaroscopy" or capillary microscopy. The site most commonly selected is the nail fold, the tissue at the base of the digital nail, but Lewis, 1927, has observed capillaries in the skin on the back of the hand and forearm, both normally and with the horny layer removed by blistering. Earlier workers are reported to have used the lower lip where the thin epidermis would seem to permit an excellent view of these small vessels. In infants the thin skin over the sternum was reported as used by Schwalm, 1934. Capillary microscopy has been used in a study of the small vessels of the oral gingiva, and, according to Pelzer, 1940, the evidence at that time gave basic validity to the technique used in this manner. But the nail fold remains the most common and convenient locus for capillaroscopy, and the following brief review applies to that part.

The gross anatomy of the nail fold is in a great measure well adapted for an examination of its contained structures. As pointed out by Callander, 1926, the vessels in this region, at the base of the nail, are seen in profile because the papillae here are arranged longitudinally.

In other portions of the skin the dermal papillae are arranged more or less vertically, and hence only the tips of the loops can be seen at the most.

Callander outlined the fundamentals of capillaroscopic technique as follows. (1) By the use of an appropriate microscopic oil the superficial layers of the skin are cleared. The oil also serves to fill in the spaces, cracks, and ridges of the skin, thereby improving the refractive phenomena. (2) The source of illumination, an essential and important part of the apparatus, is a 1,000-watt bulb. Callander suggested a typical lamp house with a reflector behind the bulb and a series of convex lenses in front. A cooling device is also needed because of the penetrating heat of the light, and a copper sulfate water cell fills this need as well as any other type of equipment. (3) The microscope should be binocular, with a magnification range of 15-61 diameters, and an objective-object working distance of 30-54 mm. The final magnification selected by Callander was 17 diameters. (4) Immobilization of the area is another important factor in this set-up. This may be accomplished by moulding the finger in modelling clay and supporting the whole hand and arm in a sand box covered in a proper manner with a protective cloth. (5) A reliable microphotographic camera is to be used for making permanent records of the observations. Callander suggested the employment of a single barrel of a Drüner stereoscopic camera. (Cinemaphotography may also be used here; Crawford and Rosenberger, 1926, described a method for this type of recording.) (6) A color filter which will give a satisfactory contrast color to the red of the capillaries should be used. Callander reported that green, made possible by the use of a potassium bichromate-copper sulfate filter solution, is the optimum contrast tint.

Duryee and Wright, 1933, in their review of modern capillaroscopy, emphasized the following: (1) immobilization of the field at heart level, (2) sufficient and cool light, applied at the correct angle of incidence and with as great an utilization of the light as possible, (3) a rapid film, sensitive to slight color contrasts, and (4) a short exposure, 1/10th to 1/25th second in duration.

Other than these general reviews of technique, the literature has not contributed much additional in the way of methods. One of the few reports which may be cited is that of Bloch and Meech, 1937, who used a triple pole carbon arc, exposing Ilford process panchromatic plates for 1/10th-1/25th of a second. Their light filter system consisted of copper sulfate cooling cells, a light bluish-green Ilford number 403 filter, and focussing condensers.

The clinical use of capillaroscopy for diagnostic purposes forms the background for three other contributions to the literature. Bordley, Grow, and Sherman, 1936, stated that, contrary to general opinion, capillaries often may be seen more clearly in Negroes than in white people. These workers also reported observing that capillary blood flow is more sluggish in the Negro than in most white people. The use of capillaroscopy as a war-time technique was outlined by Jahsman and Durham, 1943. These clinicians reported efficient recognition of incipient thromboangiitis obliterans in Selective Service candidates by the use of capillary microscopy of the nail fold. In addition to the capillaroscopic study, which was carried out according to Duryee and Wright, op. cit., the skin temperature response to external cold and heat changes was observed. Deutsch, 1941, declared that capillaroscopy, in the case of the diagnosis

of Raynaud's disease, can define the severity of the disease more accurately than the gross physical findings. This worker stated that the disease may be present before the appearance of clinical symptoms, but that abnormal capillaries can be seen when other vasomotor symptoms are not present.

DEVELOPMENTAL AND DEFINITIVE ANATOMY OF THE CAPILLARIES

The gross structures of the arterioles and venules are accepted as definite knowledge in present-day histology, but in the case of the capillary the teachings of the anatomy of this minute vessel have been challenged. A resume of the embryology and ultimate anatomy of the small blood vessel system is therefore included at this point.

According to Sabin, quoted by Krogh, 1929, the blood vascular system begins when the angioblasts differentiate from the mesenchyme of the vertebrate embryo. As the angioblasts divide and increase, they form syncytial masses, which liquefy centrally, resulting particularly in the plasma, and sprout to form new vessels. As the sprouts from the primordial vessels elongate, they join similar groups and thus form plexuses. The vessels are first seen as endothelial tubes with which adventitial cells are later associated.

The growth of capillaries in the living and mature animal undoubtedly gives many clues to the prenatal development of these vessels. The Clarks,

1939, reported their observations on capillary growth in the adult rabbit, stating that their findings agreed with those of previous workers on amphibian larvae. The Clarks saw new capillaries developing from sprouts continually being sent out from preëxisting blood vessels; these sprouts quickly anastomosed into loops which, as a plexus, advanced across the observed area. A sprout consisted of an out-pocketing of the endothelium of an active capillary, followed by the extension of a solid, blindly-ending sprout which grew longer, and into which a lumen, continuous with the parent vessel, progressively advanced. The Clarks also observed the migration of endothelial nuclei from the parent vessels into the sprouts. Also noted was the merging of nuclear areas with the solid tips which subsequently remained on the capillary wall as typical nuclei, following the extension of the lumen from the base or the formation of a vacuole which later merged with the advancing lumen. Likewise observed were mitotic divisions of endothelial nuclei, as were the retraction and disappearance of capillaries with diminished circulation through them. More complete data on the extra-endothelial cells were published a year later, 1940, by these same workers. As in the amphibia, the adventitial cells on the capillary (better, the pericapillary cells) developed from the surrounding connective tissue. Fibroblast-like cells were seen to flatten out on the walls of the new blood vessels at an early stage in the rabbit, often during sprout formation. Here the cells assumed a longitudinal arrangement with their processes extending parallel with the vessel wall. The numbers of new pericapillary cells which formed in this fashion on growing capillaries appeared to vary with the number of fibroblasts present in the region outside. The subsequent fate of these new additions to the vessel wall depended on the ultimate fate of the vessel concerned.

If the vessel remained a capillary, these cells might increase slightly in number by mitosis, or there might be no increase or even a decrease in the original number of cells. Vessels which subsequently became arterioles or venules showed appropriate incremental and positional changes in the extra-endothelial cells. These findings were also made by Paula e Silva, 1940.

Leader, 1932, made a capillaroscopic study of the new-born. From his microscopic, he concluded that at birth there exists no loops, only a primitive plexus supplied by the arterioles of the deeper layers. After four to five weeks widespread saddle-shaped forms sprout from the primitive plexus, gradually developing into slender hair-pin-like loops which do not appear in large numbers until about the fifth month.

The actual structure of the definitive capillary plays an important role in much of the physiology of the vessel, as will be seen in the succeeding discussions in this paper. Krogh, op. cit., insisted on two elements in the capillary wall: the endothelial tube of squamous epithelium, one cell thick, and an outside muscular coat, represented by the supposed smooth muscle cells or pericytes, arranged in a sort of wide-meshed network. The Loeschkes, 1934, were reported as confirming the presence of the pericytes, but stating that these cells take no part in the contraction of the vessels, and not mentioning any smooth muscle similarity as reported by Krogh and others. Plenk, 1937, in the same journal, was reported to have found, between capillaries and veins of about 100 micra in diameter, a series of pericapillary cells grading from the typical branched connective tissue type into obvious smooth muscle cells. He concluded that this observation rendered more likely the concept

of capillary contraction by the pericapillary cells.

The Clarks, 1943, characterized the adventitial or pericapillary cells as "potential contractile elements," but could not elicit from them responses to mechanical or electrical stimulation. These workers admitted that once the pericytes increase mitotically and become circular smooth muscle cells around the capillary, the vessel is no longer a capillary but has become an arteriole. Zweifach, 1939, distinguished between two types of what he called capillaries: the muscular or arterio-venous capillaries, from which branch the second type, true and non-muscular capillaries. The former has continued on it the musculature of the arteriole. But, as the present writer has implied in a succeeding section, this new idea may be a mere restatement in different words of a previously established concept.

Michels, 1936, comes the nearest, of all writers, to stating the most modern conception of the capillary. He emphasized that the capillary is a naked endothelial tube. He did not confirm in his study the muscular nature of the pericapillary cells, and recommended that "since no one knows what a 'Rouget cell' is, the term should be dropped." In place of this name, Michels offered the term pericyte to be applied to pericapillary connective tissue cells. He concluded that, morphogenetically considered, pericytes comprise the following: primarily, fibrocytes and undifferentiated mesenchymal cells; secondarily, histiocytes, resting wandering cells, emigrating lymphoid cells, and sloughed off endothelial cells. Michels also rejected the view of Jones, 1936, that capillary endothelial cells represent elongated spirally twined circular muscle cells carried over into the capillary bed.

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CAPILLARY CONTRACTILITY

Previous to the time of Krogh, according to that worker in 1929, the smallest blood vessels were considered as passive structures, the circulation through them depending upon the activities of the contractile arterioles supplying these capillaries. Krogh, however, challenged this physiology logically when he suggested that this mechanism may be all well and good under conditions of increased pressure, but under less demanding pressures, the blood supply to the capillaries and therefore to the tissues would be inadequate. Krogh goes on to point out that Philip and Hastings in their work of 1804-1820 observed a contraction of the small blood vessels, but did not distinguish between the arterioles and the capillaries. Stricker in 1865, observing the frog nictitating membrane, is declared by Krogh to have been the first to have observed independent contractility of the capillary, but whether Krogh drew a generalization from Stricker's report, one cannot tell from his writing. It is suspected that, in the light of contemporary research, he did.

Krogh, then, proceeded to formulate his Rouget cell hypothesis of capillary contractility. The Frenchman Rouget in 1873 reported that he saw, in the capillaries of the frog hyaloid eye membrane, oblong nuclei on the outer surface of the endothelium. These cells possessed elongations which surrounded and intimately embraced the vessel as the hoops of a barrel. Several years later Rouget reported similar observations on young newt larvae, stating that these cells were seen to contract. The final

verification of Rouget's histology was made, according to Krogh, by one of the Danish scientist's students, Vimtrup, 1922, using the tongue of the frog. Dr. Vimtrup, an histologist, reported in detail the morphology of the Rouget cells, presenting what he took to be concrete evidence for their observed contraction.

Aside from the Krogh school, other workers supported the Rouget cell and active contraction of the capillary, at least in certain species. Representative of this research was the contribution of the Clarks, 1925, based on amphibian larvae. From their work on the tadpole, they reported both active and passive contraction of the capillary endothelium; but the writers also declared that any active contraction they saw was independent of a peripheral cell on the capillary, specifically the Rouget cell. Contractions were observed in vessels before any Rouget cells had developed on their walls.

In the years following Krogh's 1929 review a new interest in the problem of capillary caliber changes began to evidence itself, and criticisms of the Rouget-Krogh-Vimtrup hypothesis began to weaken this theory. Zweifach, 1934, repudiated the previous concepts, stating that the capillary endothelium itself is the contractile element in the capillary system, and that he found no adjoining structures to be concerned with the functional relaxation and contraction of the capillaries. His experimental observations were made upon the frog mesentery, where the Rouget cells were said to be found, and upon the tongue, nictitating membrane, and intestinal wall of the same amphibian. Zweifach could not even report the presence of a cell or cells conforming with the previous reports, and from his experimental manipulations produced contractile changes only in the endothelium. Volterra and Schupfer, 1934, studying a number of the

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3. The third part of the document presents the results of the study, including a comparison of the experimental findings with the theoretical predictions. It also discusses the implications of the results for future research and practical applications.

4. The final part of the document provides a summary of the key findings and conclusions. It highlights the strengths and limitations of the study and offers suggestions for further research in this area.

vertebrates, were reported likewise as concluding that the capillaries of vertebrates do not possess a cellular apparatus to regulate their caliber; these workers gave credit for the mechanism involved to physico-chemical changes, especially variations in the pH, in the capillary wall and neighboring connective tissue. Field's report, 1935, tended to confirm the Rouget cell in the frog and rat, but at the same time one can sense a feeling of uncertainty in this work as to whether the Rouget cells are as responsible for capillary contraction as had been declared. Field observed that mechanical and electrical stimulation caused obliteration of the vessel lumen by the endothelial nuclei expanding into the lumen, also that the Rouget cell actively contracted, causing by its embrace of the vascular wall a constriction of the capillary. A number of other workers presented evidence, in the main, tending to upset the accepted Krogh teachings, but these have been outlined in the preceding section on capillary morphology. Such work as has been indicated above provided a background for the formulation of new concepts of the contractility of capillaries in the frog, namely those propounded by Fulton and Lutz at Boston University. In a report in 1940, later developed in his doctoral dissertation, 1941, Dr. G. P. Fulton stated the conclusions of several years' micromanipulative work on the retrolingual membrane of the frog. The most significant and important of these may be enumerated as follows: The origin of the capillary is the only place where actual capillary contractility functions; active pericapillary cells are seen at this place. Any pericytes further along, on the body of the vessel, were found to be inert, as they did not respond to either direct stimulation or indirect activation through a nerve. Stimulation of any of the small nerves in the area of the capillaries produced a response confined to a local vascular pattern; this fact with others supports the concept of a smooth muscle

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3. The third part of the document presents the results of the study. It includes a series of tables and graphs that illustrate the findings of the research. The data shows a clear trend of increasing activity over time.

4. The fourth part of the document discusses the implications of the findings. It suggests that the results have significant implications for the field of study and may lead to further research in this area.

5. The fifth part of the document provides a conclusion and a summary of the key findings. It reiterates the importance of the study and the need for continued research in this field.

motor unit involved in the contractile mechanism of the small blood vessels. This new concept of capillary caliber changes being controlled by a neuromuscular sphincter mechanism at the origin of the capillary was likewise expounded in detail by Lutz, 1942.

The foregoing review of the work on the lower vertebrates has been necessary to establish a foundation for the researches on the mammal. In this high chordate group similar projects have been carried out which have established, to a far less extent, the physiology of the mammalian blood capillaries. One of the first communications on this work to follow Krogh's 1929 review was Sandison's 1931 observations on the rabbit, employing the transparent ear chamber of the Clarks. In the Clark chamber an actual living capillary bed was maintained, and its activities observed in a real-life situation. Sandison reported seeing the Rouget cells, but did not commit himself on them as contractile units. He further declared that, according to his observations and those made by the Clarks in 1931, mammalian endothelium possesses definite tonicity but exhibits no active contractility.

Rogers, 1935, experimented in vivo with the capillaries of the cat omentum. He did not report a constriction caused by mechanical stimulation of pericapillary cells, but he claimed that the capillary endothelium responded to mechanical stimulation by constricting in the area stimulated; this contraction, however, did not spread along the capillary, nor was it sufficient to stop circulation. The work of Field, 1935, was done on the rat as well as the frog and has been evaluated above. Beecher, in the first of two reports, 1936a, definitely affirmed the Rouget hypothesis for the rabbit. Using a modified Clark window technique described above, he claimed that the capillary blood flow is obstructed in two ways: (1) by

constriction of the lumen through the contraction of the Rouget cells; (2) blocking of the stream by the swelling of the nuclei of the endothelial cells. He also stated that spontaneous contraction of the capillaries is found in the Amphibia, but admits that evidence for this phenomenon in mammals is open to question. In a following paper, 1936b, also published from the Krogh laboratory in Copenhagen, Beecher sought to establish the sympathetic (autonomic) control of the Rouget cells and its influence upon the endothelial cells. He again used the window technique on rabbits' ears and studied the effect of such factors as local cold and heat (provided by the especially devised chamber described previously), prolonged cooling, general body cooling, induction shocks, anoxemia, fright and pain, etc. He again reported activity of the Rouget cells and endothelial nuclei in producing caliber changes in the vessel. Aside from these results it is difficult to see how this worker established sympathetic nervous control of the Rouget cell, assuming such to exist.

Michels, 1936, studied fixed preparations and Berlin blue intravitaly stained whole mount preparations of the rabbit omentum, but from these he could not find any evidence supporting the claim of myogenicity advanced for the Rouget cell. He reviewed the previous literature which likewise showed no evidence of Rouget cell contractility. (1) These cells do not show myofibrils, nor has the transition from muscle cell to Rouget cell ever satisfactorily been explained. (2) The fact that these cells store vital dyes would tend to mark them as connective tissue cells. (3) They are modified sloughed-off endothelial cells, because the cytoplasm of the Rouget cell can only be seen when capillaries appear to be contracted, and when dilated, the processes of these cells are faint or indistinguishable. (4) They are not visible in fixed preparations, and, in vital preparations,

they cannot be distinguished from other cells. (5) The number of the Rouget cells would not seem sufficient to cause capillary constriction, while during apparent constriction, the endothelium appears to move away from the Rouget cell. (6) They cannot be found in higher animals. (7) When directly stimulated in vivo, mechanically or electrically, they do not cause capillary contraction. (8) Definite innervation of these cells has never been substantially proved. (9) Many reports show that these cells have often been mistaken for pericapillary nerves, that is, nucleated segments of Remak fibers. The extreme length of some Rouget cells would seem to favor this idea. (10) Since capillary endothelium itself has been observed to have an inherent power of contraction, the Rouget cells are not necessary for the constriction of these vessels.

Jones, 1936, studied the capillaries in the iris of the albino rabbit, using a methylene blue intravital technique. He concluded that the capillary consists of a neuromuscular mechanism of the same nature as the walls of the larger blood vessels and contractile viscera generally. Jones asserted that Rouget cells belong to the nervous element and not the contractile portion of this mechanism, and that the contractile elements are ordinary smooth muscle cells. Jones' mammalian work, however, was done on fixed preparations and consequently did not show the morphology from a physiological point of view.

Zweifach and Kossman, 1937, observing the white mouse mesentery, intestinal wall, and ear, proposed a new capillary concept. These men reported seeing two types of capillaries: "non-muscular or true capillaries" and "muscular or arterio-venous bridges." The AV bridges were described as possessing pericapillary muscle cells and maintaining a continuous flow of blood within themselves, while the non-muscular vessels were

characterized as lacking both of these elements. Spontaneous, rapid alterations of diameter, such as is true of the arterioles, were not seen in either of the types. In the case of the AV bridges, certain perivascular cells caused a partial constriction of the lumen. Direct stimulation of the capillary endothelial cells resulted in a localized contraction of these cells, but this did not involve the entire circumference of the vessel, and did not occlude the blood stream in its circulation. Zweifach, 1939, extended his observations, working with frogs as well as the mouse. He reaffirmed his two-type thesis, denying that contractile perivascular elements were present on his "true capillaries." A further report, 1940, while not specifically naming the animal studied, described active contractility in the arterioles, and to a less extent in the arterio-venous bridges (or "muscular capillaries" of Zweifach), but did not ascribe active constriction to the true capillaries.

Ferguson, 1937, following up Zweifach's 1937 study, confirmed the idea of pericyte contractility, but added that the evidence is all against their contraction in any essential manner affecting the caliber of the underlying capillaries.

E. R. and E. L. Clark, 1940, studied the extra-endothelial cells in the vascular bed of the living rabbit's ear. To them the longitudinally arranged peripheral cells on capillaries and small venules showed no evidence of contractility. While not specifically stated in the report, the Rouget-Krogh-Vimtrup idea of pericytic contractility, one may deduce, is rejected. Contemporary with this work of the Clarks came a communication from the English investigators Sanders, Ebert, and Florey, 1940. These men definitely repudiated the Rouget theory, but at the same time averred that capillary contractility occurs in the rabbit ear, that this

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contraction is under the control of the sympathetic nervous system, and that endothelial swelling causes obliteration of the vessels.

The Clarks have more or less dismissed the whole matter of capillary contractility. In their most recent contribution, 1943, these workers declared that the control of the peripheral circulation in the mammal resides in those blood vessels which have muscular walls and intact nerve supplies. Again using their in vivo chamber technique, the Clarks found that sporadic changes in the caliber of the capillaries and venules were passive and secondary to changes in the blood flow caused by the active constriction of vessels with a neuromuscular mechanism. What simulated capillary contraction was observed in distal portions of terminal arteries and in the nearest vessels supplied by them, the pre-capillaries.

The whole concept of capillary contractility, however, can never be dismissed from the minds of some clinicians, until the use of certain terms has been put on a precise and exact basis. For example, the very word "capillary" connotes the clinician any of the small vessels. Two recent contributions may be cited in this point. Macfarlane, 1941, in a critical review of hemostasis, defined an interesting and new analysis of this vital mechanism, but including in his theorization the idea that capillary contractility is an essential factor. If we assume that capillaries constrict, as Macfarlane does, we should have no quarrel with the author of this new idea. In the light of all the work done in vertebrate vascular physiology, however, it seems a little short of the truth to teach capillary contractility when such a phenomenon has not been verified by a host of workers. Incidentally, Macfarlane bases his belief in active capillary contraction upon capillaroscopic observations on the human nail fold. Here he saw the minute vessels disappear upon stimulation,

the stimulation resulting from injury caused by the introduction of a glass fiber into the skin. Although he has reviewed the various possibilities for this effect, he holds that the vessel actively obliterated its own lumen. Hyndman and Wolkin, 1941, two American clinicians, likewise either illustrate their belief in active capillary caliber changes or a misuse of the word capillary in their report on the autonomic mechanism of heat conservation and dissipation. One is tempted to speculate that even Zweifach's new concept of capillary types may detract from a clear understanding of the capillary as a naked endothelial tube primarily patterned as a semi-permeable membrane.

THE NERVOUS CONTROL OF THE PERIPHERAL CIRCULATION

The control of the peripheral circulation, that is, the innervation of the small blood vessels, is to be considered a most important and vital phase of the vascular physiology. Krogh (1929), assuming active contractility on the part of the capillaries, stated that, as shown by his predecessors, nerve fibers accompany the capillaries. Usually observed were two fine, non-myelinated fibers running along each capillary and communicating by several anastomoses crossing the vessel. These nerves were reported as showing small swellings at irregular intervals, but ganglion cells were not found. Woollard, 1926, in a report representative of the early research on small blood vessel innervation, used intravital methylene blue staining. He concluded that medullated nerves are found most abundantly on the peripheral vessels. These end by collaterals, not only on the vessels, but in the adjacent tissues. Woollard could not find

complete innervation of the average capillary bed. What innervation was found, he claimed was derived from sympathetic fibers, no evidence of medullated nerve stimulation being present.

A study, more physiological than morphological, was made by Hartman, Evans, and Walker, 1929. These workers, examining the sartorius muscle in the living cat, noted definite dilatations of capillaries, but did not observe an opening and closing of these vessels. Faradic stimulation of the femoral nerve usually brought about a dilatation of the capillaries, sometimes constriction of the arteries and veins. Similar stimulation of the sympathetic nerve also caused capillary dilatation. Reflexes, such as is induced by the application of cold, heat, or electricity to the abdominal skin, also provoked a widening of the capillary lumen. A study of various agents and their effect on the blood vessels brought these authors to the conclusion that the typical reaction of capillaries to any but harmful stimuli seems to be dilatation.

Michels, 1935, observed that in the omentum of the rabbit, numerous non-myelinated nerves are distributed in a plexiform manner along the course of the capillaries. These capillary nerves showed an intimate relation to the capillary wall, frequently touching it, running parallel, crossing over and under and accompanying these small vessels. Michels, however, in no instance could find free endings, knob-like in appearance, on the endothelium. Since many capillaries have no nerves associated with them, and since there seem to be no terminal endings present, this worker concluded that capillary innervation is accomplished as a physiological unit, the mechanism being a closed nervous syncytium functioning at contact points with the endothelium. Michels classified the capillary nerve fibers

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as plasmodial nerve strands, formerly called Remak fibers. He could not find, in either fixed preparations nor in vitally stained material, any evidence of the sympathetic innervation of the Rouget cells, and stated also that nucleated segments of pericapillary Remak fibers have been often mistaken for pericytes.

Michels' suggestion of a physiological unit in the mechanism of blood vessel control suggests the work of Fulton and Lutz, not on mammals, however, but on the Amphibia. In their various contributions (Fulton, 1941; Fulton and Lutz, 1940, 1942; Lutz, 1942), these men have shown the possibility of smooth muscle motor units in the contractile small blood vessels of the frog. In stimulating by brief faradic shocks, using micro-electrodes, Fulton and Lutz generally observed a diphasic response, dilatation followed by constriction, of arterioles, pre-capillaries, and muscular capillary origins. These individual responses were limited to a small portion of the total vascular area of the preparation used (retro-lingual membrane). Because of the restriction of this reaction, it was concluded that the nerve plexus, shown to be present in especially stained preparations, is physiologically discontinuous, and that this suggests the concept of a smooth muscle motor unit. A recent confirmation of the Fulton and Lutz concept was made by Levinson and Essex, 1943.

The Rouget cell has been interpreted as a nervous structure. Jones, 1936, concluded that the typical Rouget cell is a unit of the neurilemma together with the accompanying nervous filament, and its branches as these appear in an exceptional position. Jones denied that the cell is contractile, but stated that it is motor to another element present in the system.

Beecher, 1936b, attempted to establish autonomic (sympathetic) control of the capillary wall by subjecting the observed vessels to varying environmental changes, particularly in the temperature. The blood vessels observed by him responded to temperature changes by reducing or stopping the circulation through the capillaries. Since temperature control had previously been shown to be subject to the sympathetic nervous system, Beecher concluded that the reactions he saw were motivated by that system. More recent and substantial evidence for the role of the sympathetic nervous system was given by Sanders, Ebert, and Florey, 1940, who reported active vessel contraction under the control of the autonomic system. By stimulating the peripheral end of the cervical sympathetic chain, a swelling of the endothelial nuclei resulted, according to these workers. Engel, 1941, showed that the sympathetic nerves are involved in the mechanism of permeability, but this data will be taken up in more detail in the discussion of capillary permeability. Clinical evidence for indirect autonomic control of the capillary circulation is advanced by Hyndman and Wolkin, 1941. These workers propose the presence of special "capillary" dilator fibers in the anterior spinal roots. Using sympathectomized human subjects, these men demonstrated the influence of the sympathetic system in instances of body adjustment to temperature changes. After a study of the evidence, however, the conclusion is reached that, under ordinary and average conditions, the body temperature, as far as the skin is concerned, is undoubtedly maintained largely by the responses of the vessels themselves to external stimuli. The central sympathetic mechanism functions more strongly when the need is extreme, and also for the utilization or integration of the entire skin surface for heat conservation or dissipation when only a part is subjected to a changing temperature. Levinson and Essex, op. cit., studied also the effect of the

sympathetic system on the small vessels. As in the results of Sanders et al., op. cit., stimulation of the peripheral end of the cut cervical sympathetic chain produced marked constriction of arterioles (not capillaries, as Sanders reported). On the other hand, stimulation of the peripheral end of either the dorsal or great auricular nerve did not cause a consistent reaction. After denervation, a definite dilatation of all the small vessels appeared, but a return of vascular tone occurred subsequently.

The Clarks, 1943, confirmed their previous work, showing that the control of the mammalian peripheral circulation is based on the active contractility of arteries, arterioles, arterio-venous anastomoses, and a few larger veins, provided the nerve supply of these vessels is intact. While spontaneous contractions and those following stimulation were absent in arteries whose nerve supply was damaged, contractions were seen to occur following the injection of adrenalin and horse serum and local mechanical pressure.

PERMEABILITY

Undeniably the most important function of the capillary blood vessels is that of the exchange of the metabolic products of the organism. The basic principle of the modern concepts of permeability physiology is that propounded by Starling, 1896. This doctrine stated that the impermeability of the capillary endothelium for blood colloids is the basis of the mechanism for the absorption of isotonic solutions of crystalloids into the circulation; or, that fluid exchange is dependent on the balance

1. The first part of the report deals with the general situation of the country and the progress of the work during the year. It is divided into two main sections: the first section deals with the general situation of the country and the progress of the work during the year, and the second section deals with the specific results of the work.

2. The second part of the report deals with the specific results of the work. It is divided into three main sections: the first section deals with the results of the work in the field of agriculture, the second section deals with the results of the work in the field of industry, and the third section deals with the results of the work in the field of commerce.

3. The third part of the report deals with the conclusions and recommendations. It is divided into two main sections: the first section deals with the conclusions and the second section deals with the recommendations. The conclusions are based on the results of the work and the recommendations are based on the conclusions.

between the colloid osmotic pressure (drawing fluid from the tissue spaces) and the hydrostatic or blood pressure (filtering fluid from the capillary blood). All of the recent workers on permeability have accepted this doctrine and have used it as the starting point for their own researches (Landis, 1934). In the summary of the present knowledge of vascular permeability, Landis' three general properties of the capillary wall may be cited: (1) An enormous total area for interchange between the blood and tissue spaces; (2) permeability to fluid which is many times greater than that of certain cell membranes so far studied quantitatively; (3) the physical characteristics of an inert (in the sense of non-secreting) membrane permeable to water and crystalloids, but relatively impermeable to the plasma proteins.

Some students have attempted to explain permeability phenomena from a morphological point of view. Swindle, 1936, proposed a "seep valve" mechanism for capillary exchanges, naming two specific kinds of these valves. The first, according to this writer, is a cylindrical meshwork of connective tissue fibers in the perivascular space of each vessel. When the vessel, in normal tissue, is maximally dilated, the seep valve is maximally compressed. Because of the impermeability of the valve itself, and because it closes what Swindle denotes as "fenestrae" in the wall of the vessel, very little or no intravascular fluid passes into the tissues. In contrast, if the vessel constricts, the cylindrical valve opens up, no longer blocking the fenestrae and also being itself more permeable. Whether liquid enters or leaves the vessels depends upon whether the liquid pressure is higher in the vessels or in the extravascular tissues. Swindle's second variety of permeability valve is found in the perivascular debris in

inflamed areas, this debris forming an one-way seep valve preventing the in seep of liquid only. The author made these studies by use of various injection methods in such tissues as heart, intestine, and skin of lower mammals and vertebrates.

Chambers and Zweifach, 1940, offered another interpretation of permeability control. From histological studies these workers concluded that an important role of the endothelial cell is the continual secretion of an intercellular cement, the chemical stability of which controls the permeability of the blood vessel. Their study, however, was done on the frog and not on a mammal. Zweifach, 1940b, presented the following principles which he believes to be of significance in this problem. (1) The extreme thinness does not affect the selective nature of protoplasmic permeability as found in the capillary wall; also, the permeability of the endothelial membrane may be explained without taking into account the permeability of the individual cells. (2) Intercellular cement is the greatest significant factor in permeability processes. (3) Coating properties of the plasma colloids have possibly an extremely important function in liquid transfer. Zweifach suggests that the plasma proteins clog the pores of the filter-like vessel. (4) Zweifach's hypothesis of muscular and non-muscular capillaries is emphasized. The division of the capillary system into these two kinds of vessels seems to provide a basis for a more efficient distribution of dissolved nutriment.

Having considered the anatomical or inherent forces which may control permeability in the capillary, we may now review the influence of certain external agents on permeability. Much attention has been given to histamine (B-iminoazolyethylamine). To the pharmacologist, histamine is

a powerful dilator of the capillaries; yet increased amounts of the substance may cause dilatation to occur to such an extent that the permeability of the vessels is altered. As a result, there is a loss of the plasma protein fraction and fluid through the vessel wall into the extracellular spaces. (Goodman and Gilman, 1941.) Many confirmations of these effects have been reported in the literature. Puddo, 1934, was reported to have found that histamine in a dosage of 1-4 mgms/kgm body weight caused a definite increase in blood concentration, with little change in the plasma protein. An increased dosage of histamine, up to 10 mgms/kgm, was followed by a greater concentration of blood and a decrease in plasma protein. Puddo also observed that albumen passes through the capillary wall more readily than globulin.

According to reports in the literature, histamine seemingly has another effect which may or may not be related to the permeability function of the capillary. Vannotti and Gukelberger, 1935, applied by cataphoresis histamine solutions to the hairless skin of the hind legs of rabbits every 2 days for 22, 29, or 67 days. These workers reported finding in the muscles a considerable increase in the capillaries and vascular anastomoses.

Among the laboratory procedures for estimating capillary permeability, a more common method is the trypan blue test, and in this histamine seems to play an important role. Colloidal dyes injected intravenously normally escape from the circulation relatively slowly and stain all the tissues slowly. In inflamed areas the rate of diffusion is so increased that the surrounding parts become deeply stained, creating a clear contrast with the less darkly stained background. Histamine gives a positive reaction in the trypan blue test. Rocha e Silva and Dragstedt, 1941, pointed out that the

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positive reaction secured in the case of many other agents is probably due to their histamine-liberating properties in living tissues. These workers emphasized that acetylcholine does not give a positive trypan blue reaction.

The rate of filtration through the vessel wall has been deduced from plethysmographic observations by White and Jones, 1939, following the method of Landis and Gibbon, 1933. White and Jones declared their technique to be readily applicable to studies where changes associated with other physiological variations in the same person are important.

That capillary permeability may be under sympathetic nervous control was demonstrated by Engel, 1941, in perfusion experiments on dogs, cats, and rabbits. This worker studied the dye penetration from the blood through the synovial membrane of the knee joint. In each animal both knees were used; one as a control with the innervation intact, the other deprived of its sympathetic nerve supply by a unilateral lumbosacral sympathectomy. Changes in the local blood flow were measured thermoelectrically. Data obtained showed that in the majority of both acute and long-term experiments, in spite of marked dilatation, the dye excretion was considerably reduced in the sympathectomized knee. Engel pointed out that this nervous mechanism involving both caliber changes and permeability is of a compensatory nature, a permeability effect tending to counteract or balance any vasomotor changes which may take place.

The selectivity of the capillary membrane and its responses to a number of various substances has long been an important problem. Field and Drinker, 1936, noted in experiments on unanesthetized dogs that visible particles of calcite, 1-2 micra in size, left the blood system and were recovered in the animal's foot lymph. In the rabbit, pneumococci injected

1870-1871

1872-1873

1874-1875

1876-1877

1878-1879

1880-1881

1882-1883

intravenously appeared rapidly in the lymph of the thoracic duct, neck, and foot. These workers also observed that in extravascularization of erythrocytes to the lymph, no extra leakage of blood proteins accompanied this escape of red cells. Microfilariae 40 micra long and 5 micra in breadth were found in the lymph of the thoracic duct and leg and in the cerebrospinal fluid. Field and Drinker compare this unmistakable passage of particulate matter to the movement of a mercury globule through a gelatin film; the movement of the globule leaves no trace of damage, and the membrane as a membrane has retained its own integrity.

Marble, Field, Drinker, and Smith, 1934, found evidence that permeability of the blood capillary wall to lipid substances other than cholesterol is slight, but is definite and greater than that to cholesterol itself. The peripheral (cervical) lymph of the normal fasting dogs serving in these experiments contained, on the average, per 100 c.c. of lymph: cholesterol 56 mgms, fatty acid 239 mgms, total lipid 305 mgms. These values were, respectively, 41 percent, 54 percent, and 52 percent of those for cholesterol, fatty acid, and total lipid in the blood plasma of the same dogs, the blood and lymph samples having been obtained nearly as simultaneously as possible.

The permeability of the capillaries to calcium was examined by Keys and Adelson, 1936, in human subjects, and the conclusions reached stated that the capillary membrane is relatively impermeable to the calcium content of the blood. In the study normal young men were exercised to exhaustion in one minute. Their blood was sampled immediately before and after the workout and at intervals during the recovery. Changes in the calcium content were found to parallel changes in the plasma protein concentration, and it was therefore concluded that these changes were due to water

exchanges between the blood and tissues.

Abell, 1939, reported on protein permeability in the rabbit ear capillaries. He concluded from his observations that mature blood capillaries, permeable to protein, are less so than are growing capillaries. This worker, employing the "moat" ear chamber, analyzed the contents of the chamber, which contained a mammalian Ringer's solution and nitrogen products which, over a period of time, had diffused from the naked vessels into the moat liquid. Calculated were the amounts of total nitrogen passing through per square millimeter of endothelial surface per 24 hours, as well as the protein nitrogen.

An interest in the relation of the endocrine secretions to the physiology of the smallest blood vessels has been witnessed by a relatively large number of recent reports in the literature. Aylward, 1941, examined the physiological reactions of Reynals' "diffusion factor" in mammalian (beef) testicles, and concluded that this factor has the property of increasing capillary permeability. Abell and Aylward, 1941, suggested that this effect may be due to mucolytic effects of the testicular extracts. Freed and Lindner, 1941, wrote that crystalline corticosterone, desoxycorticosterone, commercial adrenal cortex extract, estrone, stilbestrol, and progesterone all produced increased capillary permeability in the rabbit. These workers postulated that the ability of the steroids to maintain the life of adrenalectomized animals is not necessarily related to their effects on capillary permeability. Menkin, 1940, however, found that an extract of the adrenal cortex inhibits capillary permeability in inflammation. Hechter, Krohn, and Harris, 1942, reported that several estrogens, as well as progesterone and testosterone dipropionate, produced a relatively specific increase in the permeability of the rat uterine and vaginal

capillaries, as shown by the trypan blue test.

The final phase of capillary permeability to be reviewed here is the subject of inflammation. The majority of recent contributions on this subject are those of Valy Menkin. Menkin, 1936, in a preliminary report, described a substance found in the inflammatory exudates of dogs and rabbits, which, when introduced into the normal skin of either of these animals, induced an immediate vasodilatation and increased capillary permeability. In a succeeding communication, 1937, Menkin proposed the name "leukotaxine" for this substance, found upon isolation to be an active crystalline nitrogenous compound. In 1938 Menkin discussed more fully the chemical nature of his inflammation factor, concluding from the evidence that this substance is probably a simple polypeptide. (Menkin's hypothesis of leukotaxine being a polypeptide was seemingly confirmed by Duthie and Chain, 1939.) Because of certain workers' attempts to identify his leukotaxine with histamine, Menkin, 1939, published evidence showing a definite distinction between the two substances. He reaffirmed his previous conclusions in 1941, stating that leukotaxine and not histamine is the primary factor concerned in the mechanism of increased capillary permeability in inflammation. Menkin, 1940, also pointed out that an extract of the adrenal cortex tends wholly or in part to inhibit the effect of an exudate or leukotaxine of increasing capillary permeability. Menkin's leukotaxine concept was confirmed by Minami and Inugami, 1940. In addition to their confirmatory findings, the Japanese workers stated that leukotaxine seems to be in greater amount in an allergic inflammation than in a non-specific inflammatory reaction.

CAPILLARY BLOOD PRESSURE

From the time of the postulation of Starling's concept of the permeability phenomenon (1896), more and more attention has been given to capillary blood pressure. Landis, 1934, in reviewing this subject, described the movement of fluid through the capillary wall as depending primarily upon the balance between the capillary blood pressure and the colloid osmotic pressure of the blood. The efficiency of this balance, however, is modified by endothelial damage, tissue pressure, temperature, the accumulation of metabolic products, and by "other unidentified factors." But, of all the factors involved in this mechanism, Landis stated that the simple physical force of the blood pressure has been more frequently neglected than any other. Landis concluded that an adequate knowledge of such an elementary force would make the search for any other factors operative in fluid balance both simple and more productive.

A study of any type of blood pressure may be made directly, by measuring the actual force of the blood stream in the vessel, or indirectly, by the external volume measurement method. (1) Direct. The direct method of measuring capillary blood pressure was embodied in the procedure of Landis, 1930. This method consists, in general, of the introduction of a fine micropipette into a capillary loop. The micropipette communicates with an adjustable manometer, and a micromanipulator moves the minute cannula in three planes. A double manometer, used for rapid and accurate measurement of both high and low pressures, was also described by Landis. The entire micropipette-manometer system ~~is~~ filled with physiologic saline

solution containing sodium citrate as an anticoagulant. Visualization of the field is made possible by use of a binocular microscope. (2) Indirect. Two types may be outlined here: plethysmography and the pressure capsule method of Danzer and Hooker. Plethysmography was utilized by the McLennans and Landis, 1942, in studying the effect of external pressure on the vascular volume of the forearm and its relation to capillary blood pressure and venous pressure. The pressure plethysmograph consists simply of a pneumatic cuff in which the arm is inserted and in which a definite known pressure can be applied to the enclosed segment of the arm. The resulting effects and measurements were used to determine the effect of graded external pressure on the volume of blood in the forearm, and these pressure-volume factors in turn were compared with previously reported direct readings of capillary blood pressure. In addition, the effect of known changes of capillary blood pressure on the pressure-volume curve was examined. A close similarity existed, these workers found, between their plethysmographic values for capillary blood pressure obtained after mathematical treatment, and values previously obtained by direct micro-injection methods. The McLennans and Landis concluded, with due precautions, that the plethysmographic method may be useful in studying the volume of blood and the pressure in the minute vessels of the forearm.

The apparatus of Danzer and Hooker, 1920, is a capsule with a floor of transparent glycerin-soaked goldbeaters' skin, attached to a mercury manometric system, including a pressure changing device. The capillaries studied, usually of the human nail fold, are observed directly through the capsule, the membrane of which rests upon the nail fold. In using this apparatus, the pressure in the capsule is raised until the blood flow stops in the capillary under observation. The capsular pressure is then slowly

reduced until the blood flow returns; the manometer reading at this point is taken to represent the capillary blood pressure. Danzer and Hooker named their device the "micro-capillary tonometer."

Eichna and Bordley, 1939, compared the Danzer-Hooker procedure to the microinjection method of Landis, op. cit. In their experimentation Eichna and Bordley observed that capillary blood pressure in the nail fold, as measured by the direct method, always exceeded the venous pressure in the hand. But measurement of the capillary pressure by the Danzer and Hooker technique failed to show any correlation with the venous pressure in the hand. It was concluded, therefore, that, of these two methods, only the direct microinjection method, although technically difficult, yields more exact information concerning the capillary blood force than any indirect method. He also characterized the direct method as permitting determination of the gradient of blood pressure in the peripheral vessels. Landis criticized the external pressure methods for merely emptying the subpapillary venous plexus and not the capillaries.

Values for a normal or average blood pressure in the capillaries have been reported in the literature, but, as Landis noted (op. cit.), the values since 1875 have ranged from 1.5 to 71.0 mm. Hg. The average pressure found by Danzer and Hooker, 1920, with their tonometer, was 22.2 mm. Hg. Landis, 1930, in the original work with the microinjection technique, found the average pressure in the arteriolar limb to 32 mms, at the end of the loop 20 mms, and in the venous limb 12 mms. This data demonstrates clearly the fall in pressure in the vascular system from the heart, through

1. The first part of the document discusses the importance of maintaining accurate records of all transactions and activities. It emphasizes the need for transparency and accountability in financial reporting.

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3. The third part of the document presents the results of the study. It includes a series of tables and graphs that illustrate the findings of the research. The data shows a clear trend of increasing activity over time.

4. The fourth part of the document discusses the implications of the findings. It suggests that the results have significant implications for the field of study and may lead to further research in this area.

5. The fifth part of the document concludes the study. It summarizes the main findings and provides a final statement on the importance of the research.

the systemic circulation, and back again. The McLennans and Landis, 1942, found values of 27, 21, and 21 mms Hg for the variations of their plethysmographic method. Eichna and Wilkins, 1942, reported the following typical values (mms Hg) determined by the direct method in normal human subjects: arteriolar limb 31.5, summit of the loop 29.0, venous limb 20.5. Eichna and Bordley, 1942, published similar findings: arteriolar limb 20, 36; summit, 25.5, 33; venous limb 14, 23.5.

Eichna and Wilkins, 1942, examined capillary blood pressure (by the direct method) following neurogenic vasoconstrictor stimuli, and found that such stimulation brought about decreases in capillary pressure of from 5 percent to 33 percent. Other observations made in this study led these men to conclude the following: (1) Although strong physiological vasoconstriction mediated through the sympathetic nervous pathways may be accompanied by a fall in digital capillary pressure, the fall is relatively slight; (2) the digital capillary blood pressure may remain at a relatively constant level during wide fluctuations in digital blood flow.

S U M M A R Y

Knowledge of the physiology of the small blood vessels in the mammal, despite the availability of certain techniques and procedures, remains to be developed and expanded. The following principles have been shown to exist.

- (1) The capillary, the smallest of all blood transporting structures,

is a naked tube of endothelium. On its periphery may be found pericytes or connective tissue pericapillary cells, whose function is unknown, except that they are not actively contractile as had been previously postulated. The morphological concept of the Rouget cell has been disproved and should be eliminated from histological and physiological teachings. The main function of the capillary is that of a semi-permeable membrane, allowing dissolved substances to pass through either into the blood or tissues. The capillary, defined in this manner, exerts no active control over its own volume. The control of the caliber changes of the capillary is resident in the arteriolar vessels which immediately precede the capillaries. The nervous control and integration of the small blood vessels is delegated particularly to the autonomic nervous system, this apparently functioning, in the case of muscular vessels, through a definite motor unit mechanism.

(2) The most important and obvious physiological characteristic of the blood capillary is its permeability or fluid exchanges. Various interpretations, such as the theories of the connective tissue seep valve and endothelial cement, have placed the emphasis for this function on a morphological basis. Other investigators describe the effects of histamine or sympathetic nervous control. The selectivity of the capillary membrane to various substances is a vital factor in this mechanism. The effect on permeability of various endocrine secretions has been shown to be definite, especially in the case of the gonadal secretions; in general, all of the

1. The first part of the document discusses the importance of maintaining accurate records of all transactions. It emphasizes that proper record-keeping is essential for the transparency and accountability of the organization. This section also outlines the various methods used to collect and analyze data, ensuring that the information is reliable and up-to-date.

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4. The final part of the document provides a summary of the findings and conclusions. It reiterates the importance of the project and the commitment of the organization to achieving its goals. This section also includes a list of recommendations for future work, ensuring that the project remains a priority for the organization.

endocrine products surveyed show a tendency to increase permeability. The relation of permeability to inflammation includes the production of a definite chemical compound which increases the permeability of the involved vessels.

(3) The function of capillary permeability depends upon, to a large extent, the blood pressure within the vessels. The pressure in the capillary appears to be of definite value, although no worker has yet established a physiological standard for it. Apparently capillary blood pressure is relatively independent of the general systemic pressure, but this has not been confirmed.

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- A B S T R A C T -

This review approaches the subject of the smallest blood vessels in the mammal from the point of view of the capillary, the smallest unit of the animal vascular system. This structure is conceived of as a naked endothelial tube patterned as a semipermeable membrane. The two chief methods of small blood vessel observation in the mammal are the Clark chamber technique for the ear and capillaroscopy of the human nail fold. These methods are described in detail, and their advantages and limitations are reviewed. Of the two, the ear chamber method has given more information on the physiology of the smallest blood vessels. The smallest blood vessels begin as mesenchymal masses in the embryo; these liquefy centrally, forming the plasma and floating elements, and sprout to form the branches of the system. Sprouting is also seen in the adult animal and appears to be the normal method of vessel formation. The pericapillary cells seen at various points on the vessel are connective tissue cells, coming from the surrounding tissues, and are not at all contractile. The true capillary has no properties of independent, active contractility. Its caliber changes are determined by the activity of the preceding arterioles, and especially of the pre-capillary. In these larger vessels a definite neuromuscular, motor unit is postulated as existing. The use of the word capillary is at the present time inexact and confusing; it should only be employed to refer to the smallest, naked endothelial vessels in the vascular system. The control of the blood vessels seems to lie in the non-myelinated nerve plexus accompanying each vessel and demonstrable by certain techniques. The autonomic system is apparently concerned in this

control. There is also evidence for autonomic control of permeability. The most important function of the capillary is its permeability. The basis of the permeability phenomenon is the Starling concept of the balance between blood pressure and colloid osmotic pressure of the blood. Permeability may be dependent upon the connective tissue seep valve described around the vessel or upon endothelial cement between the constituent cells of the vessel. Histamine, primarily a capillary dilator, will cause increased permeability in large dosages. The movement of particulate matter through the endothelium has been confirmed. Calcium is largely a non-permeable substance in the blood. The permeability of the capillary wall is slight to lipid substances. Mature capillaries are less permeable to protein than are growing vessels. The endocrine secretions, especially those from the gonads, seem to increase permeability. A definite compound, the leukotaxine of Menkin, is responsible for increased capillary permeability in inflammation. The direct and indirect methods of capillary blood pressure measurement are described. The average capillary blood pressure appears to be between 20 and 25 mms Hg. The rest of the vascular system does not appear to influence greatly the pressure in the capillaries.

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